Leptotrichia spp are typically large, fusiform-shaped, non-sporulating, and non-motile rods.[4] More recently, based upon 16S rRNA sequencing, the genus *Leptotrichia* is believed to be one of the six genera in the family *Fusobacteriaceae* in the phylum *Fusobacteria*.[4] The primary habitat of *L. buccalis* is most likely the human oral cavity, typically dental plaque. As with the other oral flora, isolation of *L. buccalis* from these sites might be indicative of its role in periodontal disease or oral cavity abscesses.[5] Systemic infections are infrequent and mostly confined to patients with hematological malignancies and bone marrow transplant recipients, with neutropenia being the common underlying factor.[6] Because of its recent classification as a *Fusobacterium spp*, we think that there should be awareness of the possibility of Lemierre syndrome in patients with Leptotrichia bacteremia.

It remains difficult to link the clinical features of our patient and the sole *L. buccalis*. Given the fact that the origin of the infection remains the tonsils in our case, where mixed anaerobes are the rule, it is possible to detect secondary organisms as incidental findings that have leaked into the bloodstream. Indeed, in a significant proportion of cases in which *F. necrophorum* is isolated, other organisms are found. It is rare in the cases of classical Lemierre syndrome. In our case, we cannot exclude the possibility of *F. necrophorum* infection. Indeed, *F. necrophorum* could have been present in our patient, but undetected. A PCR study of a typical case of Lemierre syndrome in which cultures were negative detected *F. necrophorum* DNA.[7] This observation raises the possibility that this may be the cause in other culture-negative cases or even cases with organisms other than *Fusobacterium spp* isolated. We cannot exclude the possibility of concomitant bacteria such as *Fusobacterium spp* even though it was not detected. In our case, we did not perform PCR on a blood sample to prove infection with Fusobacterium.

In summary, *L. buccalis* bacteremia, although uncommon, could be associated with post-anginal sepsis. This syndrome should be kept in mind, and CT scans of the neck or Doppler ultrasound should be performed to assess the diagnosis of venous jugular thrombosis.

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References

1. Lemierre A. On certain septicemias due to anaerobic organisms. *Lancet* 1936;**1**:701—70.
2. Golpe R, Marin B, Alonso M. Eponyms in medicine revisited: Lemierre's syndrome (necrobacillosis). *Postgrad Med J* 1999;**75**: 141—4.
3. Seidenfeld SM, Sutker WL, Luby JP. *Fusobacterium necrophorum* septicemia following oropharyngeal infection. *JAMA* 1982;**248**: 1348—50.
4. Bhally HS, Lema C, Romagnoli M, Borek A, Wakefield T, Carroll KC. *Leptotrichia buccalis* bacteremia in two patients with acute myelogenous leukemia. *Anaerobe* 2005;**11**:350—3.
5. Vemelen K, Mertens I, Thomas J, Vandeven J, Verhaegen J, Verbist L. Bacteraemia with *Leptotrichia buccalis*: report of a case and review of the literature. *Acta Clin Belg* 1996;**51**:265—70.
6. Ulstrup AK, Hartzen SH. *Leptotrichia buccalis*: a rare cause of bacteraemia in non-neutropenic patients. *Scand J Infect Dis* 2006;**38**:712—6.
7. Aliyu SH, Yong PF, Newport MJ, Zhang H, Marriott RK, Curran MD, et al. Molecular diagnosis of *Fusobacterium necrophorum* infection (Lemierre's syndrome). *Eur J Clin Microbiol Infect Dis* 2005;**24**:226—9.

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Ganciclovir therapy in an immunocompetent child with resistant fever and hepatosplenomegaly due to cytomegalovirus infection. Who and when to treat?

Primary cytomegalovirus (CMV) infections in immunocompetent humans are self-limited infections from which patients generally recover without any medical intervention.[1,2] However, CMV infections can be seen with various clinical presentations in newborns. CMV is the most common congenital viral infection, occurring in 0.4—2.3% of all live births, and is probably a common cause of mental retardation and non-hereditary sensorineural deafness in children.[3]

Postnatally-acquired CMV infection in immunocompetent patients is generally subclinical but may sometimes give rise to a mild and self-limited mononucleosis-like syndrome.[4] The occurrence of CMV disease in transplant recipients and patients with AIDS is well described. CMV can cause severe pneumonitis, hepatitis, chorioretinitis, iridocyclitis, and pancreatitis with possible life-threatening multi-organ manifestations in immunocompromised persons.[5—7] We present herein the case of a 30-month-old immunocompetent girl with severe CMV infection with multiple organ involvement, who was successfully treated with ganciclovir.

A previously healthy 30-month-old girl was admitted to our hospital with fever, diarrhea, and abdominal distention of three-month duration. She was born of a healthy mother at 39 weeks of gestation (birth weight 2800 g) and had been breastfed for 4 months; at the age of 21 months, she had started attending a daycare center. Her temperature on admission was 38.5 °C, her heart rate was 110 beats per minute, and her blood pressure was 100/60 mmHg. Physical examination

revealed abdominal distension and hepatosplenomegaly (the size of her liver was 10 cm and spleen was 7 cm at the midclavicular line). Laboratory tests showed mild hypochromic microcytic anemia with a hematocrit of 25.4%, hemoglobin of 8.7 g/dl, and a normal platelet count (316×10^9/l). The total white blood cell count was 11.7×10^9/l with 28% segmented granulocytes, 54% lymphocytes, and 18% monocytes with 7% band formation. Bone marrow aspiration revealed megaloblastic changes, increased numbers of histiocytes, vacuolization in erythrocytes, and myeloid series. The erythrocyte sedimentation rate was 28 mm/h (normal: 0–10) and C-reactive protein level was 3.25 mg/dl (normal: 0–0.8 mg/dl). Her biochemical parameters were 42 U/L AST (upper normal: <40 U/L) and 34 U/L ALT (upper normal: <40 U/L). Her immunoglobulin levels including IgG, IgM, and IgA were all within the normal range. A peripheral blood smear for plasmodium was normal. Sequential cultures of blood, urine, and bone marrow were negative for tuberculosis bacilli, salmonellosis, brucellosis, leishmaniasis, and other bacterial and fungal infectious diseases. Serology for hepatitis A, B, C, HIV, parvovirus, Toxoplasma, Salmonella, and Epstein–Barr virus (EBV) infections were all negative. CMV IgM and CMV IgG were positive. The CMV PCR in blood samples (plasma CMV PCR) was 8260 copies/ml while in urine the CMV viral PCR was 1740 copies/ml. Laboratory tests from the mother showed her to be CMV specific IgG-positive. Abdominal ultrasonography revealed hyperechogenic lesions that suggested a hemangioma with 1.5 cm diameter in the left lobe of the liver and hepatosplenomegaly. A liver biopsy showed rare mononuclear cells in the portal area, necrosis in two sections, and a few inflammatory cells, but no CMV inclusions were seen. Due to the child's deteriorating state, ganciclovir therapy was initiated (10 mg/kg/day in two divided doses) and continued for 21 days. On the 5th day of therapy the fever had resolved and on the 14th day hepatosplenomegaly had significantly resolved. Ganciclovir was well tolerated in our patient and she did not experience toxicity. After completion of the therapy, both urine and blood PCR samples were CMV-negative. During her follow-up, sixth months and one year later, she had no fever and no hepatosplenomegaly. Her blood CMV PCR was negative.

Primary CMV infections rarely give rise to clinical illness in immunocompetent persons. CMV causes a mononucleosis-like syndrome with clinical features such as prolonged fever, myalgia, and cervical lymphadenopathy. EBV and early HIV infections should be differentiated in such a case.[4,8,9] Several complications or associated manifestations such as biochemical or clinical hepatitis, skin rash, colitis, pneumonitis, adrenalitis, myocarditis, and, rarely, encephalitis or other involvement of the central nervous system (CNS) have been described in immunocompetent patients with CMV infection.[10] Although it is extremely rare, severe and even fatal CMV infections have been reported.[2] Faucher et al.[11] performed a retrospective analysis of 116 adult hospitalized patients and outpatients, and reported that fever was noted in 99% of patients, with a mean duration of 21 days. Fifty-one percent of those patients had headache, 46% had myalgia, and 36% had splenomegaly. Respiratory and neurological symptoms were noted in 8% and 1% of patients, respectively.

Almost all reported cases of CMV infections in immunocompetent patients have been self-limiting, although there have been some sporadic cases, our case included, where the clinical condition is prolonged and there is deterioration for which treatment might be needed, despite an effective immune system. In this group of patients, treatment indications are still not clearly defined. Since primary CMV infection in immunocompetent hosts is generally self-limited, no specific antiviral therapy is usually required. However, antiviral therapy can be beneficial in immunocompetent hosts, including adults with severe acute or persistent CMV infection, as reported in a limited number of cases.[12,13]

Antiviral drugs, such as ganciclovir are available for CMV infection, but they are licensed for use only in severe or life-threatening illness in immunocompromised patients.[14,15] The efficacy of ganciclovir therapy in children with CMV infection remains controversial. Ganciclovir, a guanosine analog, selectively inhibits CMV DNA polymerase, and it is the antiviral drug used to treat immunocompromised patients such as transplant recipients and AIDS patients with active CMV infection.[13] A study concerning CNS infections due to CMV reported that nearly two thirds of patients in the pediatric age group treated with ganciclovir developed neutropenia.[16] Although it is not shown in humans, ganciclovir has both gonadal toxicity and carcinogenicity in animal models.[17]

Foscarnet is the only anti-herpes drug that is not a nucleoside or nucleotide analogue. Foscarnet inhibits all known human herpesviruses, including acyclovir-resistant herpes simplex virus and varicella zoster virus strains and most ganciclovir-resistant CMV isolates. Foscarnet is associated with significant renal toxicity, and it is not the drug of choice for CMV.[18]

The prodrug, valganciclovir, an orally well-absorbed ester of ganciclovir and the amino acid L-valine, was developed to increase the bioavailability of ganciclovir. In adults it achieves ganciclovir plasma concentrations similar to those with intravenous ganciclovir. The high bioavailability and convenient dosing formulation make valganciclovir an attractive option. However, though carried out in adults, there have been no safety and efficacy trials of valganciclovir in children;[19,20] pharmacokinetics and safety issues still need to be resolved in children. Valganciclovir is likely to be an alternative oral treatment that can be prospectively studied in children.

In our case, due to the prolonged severe clinical picture and deterioration, treatment of the CMV infection with ganciclovir was started and was continued for 21 days; the patient responded to this therapy dramatically and the hepatosplenomegaly decreased remarkably. After therapy, CMV PCR became negative. Our patient's clinical outcome and response to ganciclovir therapy was similar to that reported by Hadaya et al. in a 17-month-old girl who also responded to short-course (5 days) ganciclovir therapy.[21]

CMV is transmitted vertically (from mother to infant, before, during, or after birth), horizontally (by direct person-to-person contact with virus-containing secretions especially in daycare centers and via breastfeeding in children), and via transfusions of blood products. Breastfeeding significantly influences the epidemiology of postnatal human CMV infection.[23] The virus was isolated from human milk more than 30 years ago, but the roles of milk cells and cell-free virus in transmission have remained unclear.[24] Several studies have investigated shedding of CMV into breast milk and transmission to term infants.[24] The low socioeconomic status

of our patient and the history of being cared for in a crowded daycare center could suggest the second route of transmission (by direct person-to-person contact at the daycare center) as has previously been described.[22] We considered out case to be a primary CMV infection because the complaint occurred after she had started attending daycare, but we could not exclude reactivation of congenital CMV.

In conclusion, immunocompetent persons usually recover spontaneously from CMV infections, but in exceptional cases like in our patient with prolonged fever, deteriorating state, and hepatosplenomegaly, ganciclovir therapy might be beneficial. Currently, due to the known possible side effects of ganciclovir therapy, it is indicated only in limited conditions, notably in immunocompromised patients. However, in immunocompetent patients with an unstable or clinically deteriorating condition, ganciclovir might also be considered as a treatment option.

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References

1. Taylor GH. Cytomegalovirus. *Am Fam Physician* 2003;**67**:519—24.
2. Eddleston M, Peacock S, Juniper M, Warrell DA. Severe cytomegalovirus infection in immunocompetent patients. *Clin Infect Dis* 1997;**24**:52—6.
3. Whitley RJ, Cloud G, Gruber W, Storch GA, Demmler GJ, Jacobs RF, et al. Ganciclovir treatment of symptomatic congenital cytomegalovirus infection: results of a phase II study. National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group. *J Infect Dis* 1997;**175**:1080—6.
4. Horwitz CA, Henle W, Henle G, Snover D, Rudnick H, Balfour Jr HH et al. Clinical and laboratory evaluation of cytomegalovirus-induced mononucleosis in previously healthy individuals. Report of 82 cases. *Medicine (Baltimore)* 1986;**65**:124—34.
5. Vancikova Z, Dvorak P. Cytomegalovirus infection in immunocompetent and immunocompromised individuals—a review. *Curr Drug Targets Immune Endocr Metabol Disord* 2001;**1**:179—87.
6. Vancikova Z, Kucerova T, Pelikan L, Zikmundova L, Priglova M. Perinatal cytomegalovirus hepatitis: to treat or not to treat with ganciclovir. *J Paediatr Child Health* 2004;**40**:444—8.
7. Kanno M, Chandrasekar PH, Bentley G, Vander Heide RS, Alangaden GJ. Disseminated cytomegalovirus disease in hosts without acquired immunodeficiency syndrome and without an organ transplant. *Clin Infect Dis* 2001;**32**:313—6.
8. Just-Nubling G, Korn S, Ludwig B, Stephan C, Doerr HW, Preiser W. Primary cytomegalovirus infection in an outpatient setting—laboratory markers and clinical aspects. *Infection* 2003;**31**:318—23.
9. Rosenberg ES, Caliendo AM, Walker BD. Acute HIV infection among patients tested for mononucleosis. *N Engl J Med* 1999;**340**:969.
10. Ho M. Acquired cytomegalovirus infection in immunocompetent patients. In: Ho M, editor. *Cytomegalovirus: biology and infection*. 2nd ed. New York: Plenum Publishing Corporation; 1991. p. 229—47.
11. Faucher JF, Abraham B, Segondy M, Jonquet O, Reynes J, Janbon F. Acquired cytomegalovirus infections in immunocompetent adults: 116 cases. *Presse Med* 1998;**27**:1774—9.
12. Nigro G, Krzysztofiak A, Bartmann U, Clerico A, Properzi E, Valia S, et al. Ganciclovir therapy for cytomegalovirus-associated liver disease in immunocompetent or immunocompromised children. *Arch Virol* 1997;**142**:573—80.
13. Avila-Aguero ML, Paris MM, Alfaro W, Avila-Aguero CR, Faingezicht I. Ganciclovir therapy in cytomegalovirus (CMV) infection in immunocompetent pediatric patients. *Int J Infect Dis* 2003;**7**:278—81.
14. Crowley B. Ganciclovir treatment of symptomatic congenital cytomegalovirus infection. *J Antimicrob Chemother* 2002;**50**:435—6.
15. Faulds D, Heel RC. Ganciclovir: a review of its antiviral activity, pharmacokinetic properties and therapeutic efficacy in cytomegalovirus infections. *Drugs* 1990;**39**:597—638.
16. Kimberlin DW, Lin CY, Sánchez PJ, Demmler GJ, Dankner W, Shelton M, et al. Effect of ganciclovir therapy on hearing in symptomatic congenital disease involving the central nervous system: a randomized, controlled trial. *J Pediatr* 2003;**143**:16—25.
17. Ganciclovir package insert, Hoffman-La Roche, Inc. Available at: http://www.rocheusa.com/products/cytovene/pi.pdf (accessed September 2007)
18. Chrisp P, Clissold SP. Foscarnet: a review of its antiviral activity, pharmacokinetic properties and therapeutic use in immunocompromised patients with cytomegalovirus retinitis. *Drugs* 1991;**41**:104—29.
19. Burri M, Wiltshire H, Kahlert C, Wouters G, Rudin C. Oral valganciclovir in children: single dose pharmacokinetics in a six-year-old girl. *Pediatr Infect Dis J* 2004;**23**:263—6.
20. Kimberlin DW. Antiviral therapies in children: has their time arrived? *Pediatr Clin North Am* 2005;**52**:837—67.
21. Hadaya K, Kaiser L, Rubbia-Brandt L, Gervaix A, Diana A. Ganciclovir for severe cytomegalovirus primary infection in an immunocompetent child. *Eur Clin Microbiol Infect Dis* 2004;**23**:218—20.
22. Stagno S, Cloud GA. Working parents: the impact of day care and breast-feeding on cytomegalovirus infections in offspring. *Proc Natl Acad Sci U S A* 1994;**91**:2384—9.
23. Diosi P, Babusceac L, Nevinglovschi O, Kun-Stoicu C. Cytomegalovirus infection associated with pregnancy. *Lancet* 1967;**1**:1063—6.
24. Stagno S, Reynolds DW, Pass RF, Alford CA. Breast milk and the risk of cytomegalovirus infection. *N Engl J Med* 1980;**302**:1073—6.

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